REMARKS

Favorable reconsideration is respectfully requested in view of the following remarks. Claim 32 is new, and is supported by the original disclosure, for example at page 2, lines 20-24 of the specification. Claims 23-32 are pending.

Claims 23-31 are rejected under 35 U.S.C. 103(a) as being obvious over Hashimoto et al. (WO 02/44167). Applicants respectfully traverse the rejection.

The rejection contends that one would have had a reasonable expectation of success in producing the claimed invention during the process of routine experimentation. However, when Hashimoto is considered as a whole and in view of the general understanding of the amorphous phase in pharmaceutical solids at the time the invention was made, there would not have been a reasonable expectation of success in producing an amorphous optically active isomer of lansoprazole from hydrated crystals of optically active isomer (R-isomer) of lansoprazole by routine experimentation.

In particular, at the time the invention was made, the amorphous phase of the active pharmaceutical ingredient (API) was avoided in general. As explained by Brodka-Pfeiffer et al. in "Conditioning Following Powder Micronization: Influence on Particle Growth of Salbutamol Sulfate", Drug Development and Industrial Pharmacy, Vol. 29, no. 10, pp. 1077-1084 (2003)(see also Bauer, "Pharmaceutical Solids – The Amorphous Phase", Journal of Validation Technology, pp. 63-68 (2009); for the Examiner's convenience, copies of the references are attached hereto), amorphous APIs are usually unstable, and tend to convert to the stable, crystalline state. This reaction — when it occurs in a pharmaceutical preparation — is frequently regarded as undesirable because the amorphous drug particles may have an adverse effect on the properties of the solid phase preparation during storage. Yet, as made clear by Brodka-Pfeiffer et al., there was a dearth of reports on achieving a thermodynamically stable product. Thus, in the field of pharmaceutical preparations, the amorphous state of the API was generally avoided.

Hashimoto aims to provide a more stable crystal of (R)-lansoprazole during storage as compared to the starting crystal. Hashimoto is silent as to the presence of amorphous optically active isomer of lansprazole in their stable crystal product, and fails to provide any guidance or experimental data to show that hydrate crystals of the optically active isomer of lansoprazole can be converted to an amorphous optically active isomer of lansoprazole. Given that there was sparse information on appropriate handling of amorphous solids with the aim of achieving a

thermodynamically stable product, it is clear that Hashimoto fails to provide any basis to show that there would have been a reasonable expectation of success in achieving the features of claim 23.

The Examiner refers to page 8, lines 15-23 and page 14, lines 1-5 and contends that Hashimoto teaches the claimed elements. However, when Hashimoto is understood as a whole, it is clear that none of the steps discussed at page 8, lines 15-23 and page 14, lines 1-5 correspond to the step of claim 23.

In particular, on page 8, lines 15-23, Hashimoto teaches a solid which may include a crystal phase or amorphous phase. However, Hashimoto teaches that this solid is obtained from a racemic mixture, as opposed to hydrated crystals of optically active isomer (R-isomer) of lansoprazole (see page 5, line 25 to page 8, line 17).

On page 14, lines 1-5, Hashimoto indicates that the "thus-obtained crystal" may be used as it is, or dried where necessary. However, when Hashimoto is understood as a whole, it is clear that the dried product of the "thus-obtained crystal" described on page 14, lines 1-5 is a crystal exhibiting specific peaks under X-ray powder diffraction analysis. Specifically, Hashimoto clearly indicates that the starting material in their method of obtaining a more stable crystal is a crystal exhibiting specific peaks under X-ray powder diffraction analysis (see page 9, line 30 to page 10, line 4), and since the dried product of the "thus-obtained crystal" is intended to be used as the starting material, it follows that the dried product of the "thus-obtained crystal" is a crystal exhibiting specific peaks under X-ray powder diffraction analysis.

Thus, it is clear that the discussion at page 8, lines 15-23 teaches that a solid, which may include an amorphous phase, can be obtained from a racemic mixture, and the discussion at page 14, lines 1-5 of Hashimoto teaches that a crystal exhibiting specific peaks under X-ray powder diffraction analysis can be obtained from drying a crystal. Therefore, when Hashimoto is understood as a whole, it is clear that none of the steps discussed on pages 8 and 14 of the reference correspond to the step of claim 23.

The rejection then contends that it would have been obvious to achieve the features of claim 23 during the process of routine experimentation. However, as indicated above, given that there was sparse information on appropriate handling of amorphous solids with the aim of achieving a thermodynamically stable product, the present record provides no basis to conclude that there would have been a reasonable expectation of success in achieving the features of claim

23. Moreover, in view of the general understanding that there would have been a strong possibility that the amorphous form may adversely affect the properties of the solid phase of the formulation, including its stability, any attempts to obtain an amorphous lansoprazole appear to frustrate Hashimoto's purpose of achieving a more stable crystal of (R)-lansoprazole during storage. Accordingly, claim 23 and it dependent claims are patentable over the reference.

Claims 23-31 are rejected under 35 U.S.C. 103(a) as being obvious over Fujishima et al. (WO 00/78745). Applicants respectfully traverse the rejection.

The rejection contends that one would have had a reasonable expectation of success in producing the claimed invention during the process of routine experimentation. However, when Fujishima is considered as a whole and in view of the general understanding of the amorphous phase in pharmaceutical solids at the time the invention was made, there would not have been a reasonable expectation of success in producing an amorphous optically active isomer of lansoprazole from hydrated crystals of optically active isomer (R-isomer) of lansoprazole by routine experimentation.

In particular, Fujishima likewise aims to provide a more stable form of lansoprazole (page 1, lines 13-14). Fujishima is silent as to the presence of amorphous optically active isomer of lansprazole in their stable crystal product, and fails to provide any guidance or experimental data to show that hydrate crystals of the optically active isomer of lansoprazole can be converted to an amorphous optically active isomer of lansoprazole. Given that there was sparse information on appropriate handling of amorphous solids with the aim of achieving a thermodynamically stable product, it is clear that Fujishima fails to provide any basis to show that there would have been a reasonable expectation of success in achieving the features of claim 23.

The Examiner refers to page 13, line 30 to page 14, line 16 and page 2, line 32 to page 3, line 3 of Fujishima and contends that Fujishima teaches the claimed elements. However, when Fujishima is understood as a whole, it is clear that none of the steps discussed at page 13, line 30 to page 14, line 16 and page 2, line 32 to page 3, line 3 correspond to the step of claim 23.

In particular, the rejection appears to contend that the filtrate described on page 13, line 30 to page 14, line 16 corresponds to the hydrate crystal of R(+)-lansoprazole described on page 2, line 32 to page 3, line 3 of Fujishima. However, the hydrate crystal of R(+)-lansoprazole

described on page 2, line 32 to page 3, line 3 of Fujishima clearly refers to the final stable product described on page 1, line 28 to page 2, line 15 and not to the starting materials.

On page 13, line 30 to page 14, line 16, Fujishima teaches that the amorphous phase of R(+)-lansoprazole is obtained from the racemic mixture of lansoprazole. Fujishima is silent as to whether the filtrate that is dried is a hydrate crystal of lansoprazole.

Thus, it is clear that the discussion at page 2, line 32 to page 3, line 3 of Hashimoto teaches that their final stable product can be a hydrate crystal of R(+)-lansoprazole, and the discussion at page 13, line 30 to page 14, line 16 of Fujishima teaches that an amorphous phase of R(+)-lansoprazole can be obtained from a racemic mixture of lansoprazole. Therefore, when Fujishima is understood as a whole, it is clear that none of the steps discussed at page 13, line 30 to page 14, line 16 and page 2, line 32 to page 3, line 3 correspond to the step of claim 23.

The rejection then contends that it would have been obvious to achieve the features of claim 23 during the process of routine experimentation. However, as indicated above, given that there was sparse information on appropriate handling of amorphous solids with the aim of achieving a thermodynamically stable product, the present record provides no basis to conclude that there would have been a reasonable expectation of success in achieving the features of claim 23. Moreover, given the general understanding that there would have been a strong possibility that the amorphous form may adversely affect the properties of the solid phase of the formulation, including its stability, any attempts to obtain an amorphous lansoprazole appear to frustrate Fujimoto's purpose of achieving a more stable crystal of (R)-lansoprazole during storage. Accordingly, claim 23 and it dependent claims are patentable over the reference.

Claim 32 clarifies the properties of the amorphous optically active isomer of lansoprazole and is patentable over Hashimoto and Fujishima for at least the same reasons discussed above.

In view of the above, favorable reconsideration in the form of a notice of allowance is requested. Any questions or concerns regarding this communication can be directed to the attorney-of-record, Douglas P. Mueller, Reg. No. 30,300, at (612) 455.3804.

Respectfully submitted,

HAMRE, SCHUMANN, MUELLER & LARSON, P.C.
P.O. Box 2902
Minneapolis, MN 55402-0902
(612) 455-3800

Dated: March 10, 2010

By: _____
Douglas P. Mueller
Reg. No. 30,300

DPM/ym

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 29, No. 10, pp. 1077–1084, 2003

RESEARCH PAPER

Conditioning Following Powder Micronization: Influence on Particle Growth of Salbutamol Sulfate

Katharina Brodka-Pfeiffer,[1,2] Heribert Häusler,[2] Peter Graß,[2] and Peter Langguth[1,*]

[1]Institute of Pharmacy, Biopharmaceutics and Pharmaceutical Technology, Johannes Gutenberg-University, Mainz, Germany
[2]Boehringer Ingelheim Pharma KG, Ingelheim am Rhein, Germany

ABSTRACT

Micronization is a high-energy process that induces changes in the crystallinity of materials. As a result, the crystalline structures on the particles' surface are being destroyed and amorphous areas are formed. After micronization of salbutamol sulfate to be used in dry powder inhalers, only small amounts of amorphous material are produced. Nevertheless, even these small amounts can have important effects on the physical stability of the powder. The amorphous state is thermodynamically unstable and tends to convert to the stable, crystalline state. The recrystallization process of disordered regions on the particles' surface leads to particle growth of milled particles. In this case, bridges of solid material are being formed between the individual particles, which leads to particle growth. This is an undesirable process, because particles for pulmonary administration are designed to range between 1 and 10 μm in diameter to exert respirative effect. In the present investigation, salbutamol sulfate is micronized by an air jet mill, and the generated products are exposed to different conditions. Thereafter, the best possible conditioning parameters and storage conditions for the micronized salbutamol sulfate are worked out and rated. The aim of this treatise is to demonstrate the importance of conditioning following micronization.

Key Words: Dry and wet conditioning; Storage; Salbutamol sulfate.

*Correspondence: Peter Langguth, Institute of Pharmacy, Biopharmaceutics and Pharmaceutical Technology, Johannes Gutenberg-University, Staudinger Weg 5, 55099 Mainz, Germany; Fax: 0049-6131-3925021; E-mail: langguth@mail.uni-mainz.de.

DOI: 10.1081/DDC-120025865
0363-9045 (Print); 1520-5762 (Online)
www.dekker.com

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

INTRODUCTION

In some pharmaceutical processes, such as grinding, wet granulation, tablet compaction, and spray drying, disorder of crystal structure can occur and may lead to amorphous particles or parts thereof. Amorphous regions demonstrate rheological properties of a solid state and the structure of a liquid.[1] Because of their higher state of energy, they are thermodynamically unstable and tend to convert to a stable, crystalline state. This reaction—when it occurs in a pharmaceutical preparation—is frequently being regarded as undesirable, because the amorphous drug particles may change their properties on storage. In previous publications, analytical methods for the detection of amorphous material in pharmaceutical systems were introduced.[2–5] Processes leading to changes in crystallinity also were described,[6] and the significance of these findings for pharmaceutical systems were discussed.[7,8] Until the present, sparse information on appropriate handling of amorphous solids with the aim of achieving a thermodynamically stable product has been published.

In the study described here, partly amorphous salbutamol sulfate is formed as a result of micronization with an air jet mill. Air jet micronization represents an important step for the manufacture of constituents of dry powder inhalers. Depending on the level of grinding energy, increasing fractions of amorphous material may be generated on the surface of the crystal. Problems with respect to uncontrolled particle growth may arise in those instances when the recrystallization of the micronized material proceeds in an uncontrolled manner (e.g., during arbitrary storage conditions of the pharmaceutical powder). This may have serious consequences with respect to the effectiveness of powders for inhalation, because particle growth may generate fractions of the particles with diameters outside of the respirative range (between 1 and 10 μm).

One of the techniques towards achievement of micronized powders with improved physicochemical stability is the introduction of a conditioning step following their micronization. During this process, the amorphous parts are converted into crystalline solids under storage conditions that are controlled with respect to relative humidity and temperature. These conditions aim at reducing the glass transition (Tg) of the solid material by the adsorption of water[9] and setting the surrounding temperature to values above Tg so that the molecular mobility and, consequently, the recrystallization process is accelerated.[10]

In this treatise, the influence of conditioning parameters for micronized salbutamol sulfate is investigated systematically according to Sch. 1 to discover optimum conditioning parameters for the rapid and entire conversion of amorphous to crystalline material with minimum particle growth.

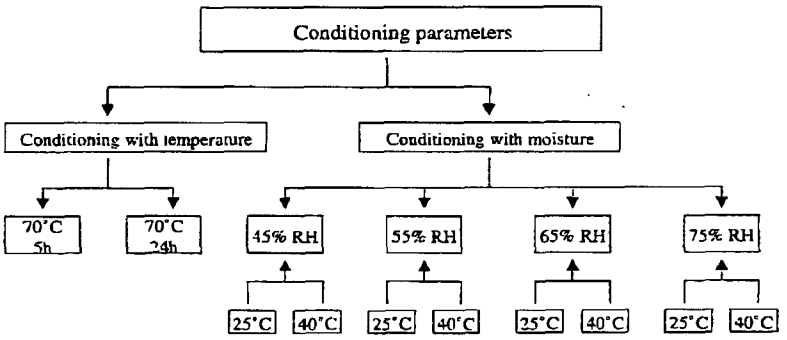
MATERIALS

Salbutamol sulfate (batch Nos. 200713, 200921, and 1001825) was supplied by Boehringer Ingelheim Pharma GmbH&Co. KG (Ingelheim, Germany). As packaging materials, a polyethylen bag, a polyethylen bag within an aluminium bag, and a twist-off-Glass were used.

METHODS

Milling

Micronized powders were prepared with a MC Jetmill 50 (Jetpharma, Balerna, Switzerland). Extant room conditions were 21°C ± 1°C and 45% ± 2% RH.



Scheme 1. Systematic evaluation of conditioning parameters for micronized salbutamol sulfate.

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

Conditioning

The micronized powders underwent different conditioning settings in a climate chamber (Weiß Klimatechnik GmbH, Reiskirchen-Lindstruth, Germany). The temperature was set at 25°C and 40°C, and the relative humidity was varied between 45% and 75%, respectively. For "dry" conditioning settings, the powders were prepared at a temperature of 70°C in a thermal oven (Heraeus, Hanau, Germany).

Recording of Humidity

The sorption behavior of the micronized and wrapped powder was measured by using a humidity sensor (Ebro, Ingolstadt, Germany).

Particle Size Analysis

The particle size distributions of salbutamol sulfate were measured by using powder laser diffraction with a Helios-System (Sympatec, Clausthal-Zellerfeld, Germany). Samples were introduced through the Rodos dry powder feeder. The supply pressure of the injector was set at 3 bar. The optical concentration reached values between 4% and 8%.

Particle Morphology

The morphology of salbutamol sulfate was examined by using a DSM 926 scanning electron microscope (Zeiss, Jena, Germany). The powders were mounted onto a plate and were sputter coated with 60 nm gold/palladium.

Isothermal Microcalorimetry

The powder was investigated using a Thermal Activity Monitor (Type 2277, Thermometric, Sweden) at 25°C. The samples were weighted into a glass ampoule and a tube was added containing a saturated salt solution. The ampoule was sealed and equilibrated in the calorimeter for 5 min before lowering it into the measuring site.

Powder X-Ray Diffraction

The Powder X-Ray Diffraction (Bruker, Rheinstetten, Germany) patterns were acquired at different temperatures using Cu-K α radiation ($\lambda = 1.5406$ Å). The data were collected over an angular range of 2–40° 2θ using a step size of 0.014° 2θ and a step time of 2 s.

RESULTS AND DISCUSSION

Conditioning with Elevated Temperature ("Dry" Conditioning)

Conditioning of the micronized salbutamol sulfate for a duration of 5 hr at 70°C did not lead to recrystallization, and therefore no stable product was formed. Such conditions have been identified as counterproductive rather, since water was expelled from the sample due to the high temperature. Water in this case serves as a plastisizer and consequently its disappearance leads to a stabilization of the amorphous state (increase in *Tg*). Therefore, no changes in the amorphous content were observed under such conditions.

With the use of isothermal microcalorimetry it was shown that the exothermal recrystallization process was delayed on account of the water displacement (Fig. 1). An increase of the thermal conditioning time for a duration of up to 24 hr had no additional effect.

Particle growth was not observed following dry conditioning. This is shown in Table 1.

With the use of x-ray powder diffractometry in vacuum and at different temperatures, it was demonstrated that amorphous salbutamol sulfate (produced by freeze-drying) did not recrystallize under exclusion of humidity (Fig. 2). Therefore, water molecules are necessary for the transformation into the thermostable state. Consequently, minimum relative humidities are essential to initiate and maintain the recrystallization process.

Conditioning with Moisture ("Wet" Conditioning)

By using isothermal microcalorimetry it has been found that relative humidities below 50% at 25°C were insufficient to achieve complete recrystallization of amorphous salbutamol sulfate within 24 hr. For

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

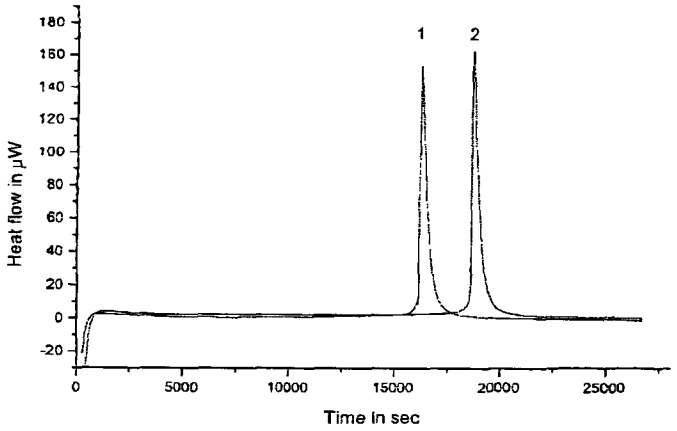


Figure 1. Isothermal microcalorimetry of a freshly micronized powder (1) and one of a dry conditioned powder at a temperature of 70°C for 5 hr (2).

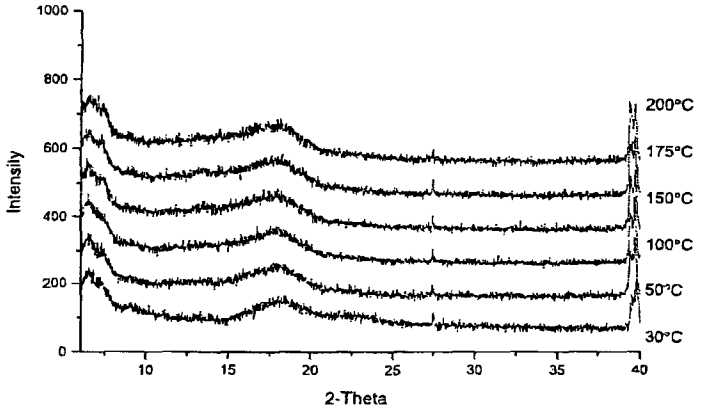


Figure 2. X-ray powder diffractometry of 100% amorphous material at different temperatures under vacuum. The material was stored at room temperature under P_2O_5.

Table 1. Particle size distribution after dry conditioning of micronized salbutamol sulfate.

	Micronized powder (µm)	Micronized powder conditioned for 5 hr at 70°C (µm)	Relative change of particle size spreading (%)
<10%	0.83	0.82	−1.2
<50%	1.94	1.90	−2.1
<90%	4.53	4.45	−1.8

example, conditioning of a sample for a 24 hr time period at 25°C and 45% RH lead to a reduction of the amorphous fraction by only 2.5% at an initial content of amorphous material of 7.7%.

When more appropriate conditioning settings by increasing the relative air humidity were used, complete recrystallization occurred; however, particle growth was inevitable in each batch investigated. The particle growth was attributed to the formation of bridges between the amorphous surfaces that took place during the recrystallization process.

By means of selective variation of humidity and temperature, the percentage of particle growth was studied. A clear tendency toward stronger particle growth was observed by an increase in relative humidity (Table 2). For example, the relative change in particle size distribution of the fraction below the 50th percentile increased from 8.5% at 55% RH and 25°C to 15.0% at 65% RH and 25°C. A less pronounced effect on particle growth was

Received Time Mar. 3. 2010 12:53AM No. 2379

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

Table 2. Dependence of particle growth on the relative humidity and temperature during conditioning.

	Micronized powder (μm)	Micronized powder conditioned (μm)	Relative change in particle size distribution (%)
24 hr 55% 25°C			
<10%	0.70	0.78	11.40
<50%	1.30	1.66	8.50
<90%	3.42	3.56	4.10
24 hr 65% 25°C			
<10%	0.70	0.82	17.10
<50%	1.53	1.76	15.00
<90%	3.42	3.67	7.30
24 hr 75% 25°C			
<10%	0.70	0.83	18.60
<50%	1.53	1.77	15.70
<90%	3.42	3.69	7.90
24 hr 55% 40°C			
<10%	0.70	0.79	12.90
<50%	1.53	1.68	9.80
<90%	3.42	3.59	5.00
24 hr 65% 40°C			
<10%	0.70	0.80	14.30
<50%	1.53	1.72	12.40
<90%	3.42	3.64	6.40
24 hr 75% 40°C			
<10%	0.70	0.84	20.00
<50%	1.53	1.78	16.30
<90%	3.42	3.69	7.90

observed by an increase in the conditioning temperature from 25°C to 40°C at constant relative humidities (Table 2).

Following conditioning for a 5-hr time period at 40°C and 75% RH, a sample of partially amorphous powder was completely converted into crystalline material. Prolongation of the duration of the conditioning process beyond 5 hr had no additional effect on the particle size distribution. Thus, it may be concluded that the final stage of the conditioning process was already reached after 5 hr (Table 2).

In summary, it has been shown that dry conditioning was not a feasible approach. The more important factor was the relative humidity, which should be maintained at 55% at room temperature for the product to recrystallize within 24 hr. This humidity level showed the smallest influence on particle growth. The most rapid conditioning was achieved at 40°C and 75% RH where a stable, entirely crystalline product was obtained already after 5 hr of treatment but with the largest increase in particle size.

Physical Stability on Storage

Storage Following "Dry" and "Wet" Conditioning

Using the methods described above, it was shown that the physical stability of the product on storage under normal storage conditions (i.e., 22°C ± 2°C; 50% ± 8% RH) was dependent on the parameters of a preceding conditioning step. With dry conditioning, uncontrolled particle growth up to 16% in terms of particle diameter was observed following 4 weeks of storage. Humid conditioning as pretreatment of the freshly milled material on the other side resulted in products that remained stable throughout the storage period (Fig. 4).

Storage Without Preceding Conditioning Step

The assessment of particle growth of non-conditioned material was conducted under different methods of storage. When freshly micronized powder was stored in an open TWO-Glass at 21.5°C and 42% RH, the use of isothermal microcalorimetry indicated a gradual loss of amorphous content in the sample over a storage period of 4 weeks (Fig. 3). When salbutamol sulfate—stored in a simple PE-bag—was evaluated for its amorphous content at different storage times, a continuous decrease was observed. Recrystallization was significantly minimized when micronized salbutamol sulfate was wrapped in a PE-bag plus an aluminum bag. This observation can be explained by the fact that the latter packaging material showed the least overall water permeability.

To assess particle growth of nonconditioned samples during storage, 50 g of freshly micronized material was wrapped in a PE-bag and stored at 22°C ± 1°C and 45% ± 5% RH for a total period of 3 months. After 1, 2, and 4 weeks as well as after 3 months, samples were collected and analyzed for their particle size distribution and amorphous content. The powder treated under these conditions showed significant particle growth.

By incorporating a humidity sensor into the PE-bag, the sorption behavior of the micronized powder was monitored. For this experiment, ~30 g

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

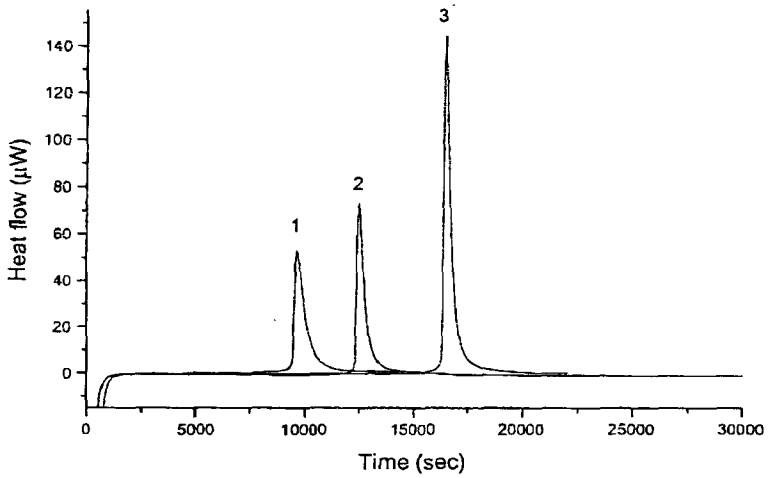


Figure 3. Microcalorimetry of micronized unconditioned salbutamol sulfate on storage in an open TWO-Glass at room temperature (21.5°C, 42% RH): Amorphous amounts following 1 (3), 2 (2), and 4 (1) weeks of storage. The amorphous contents were 6.5%, 5.4%, and 4.5% following storage for 1, 2, and 4 weeks, respectively.

of freshly ground material were wrapped in a PE-bag together with a humidity sensor. The bag was closed and stored at 22°C ± 1°C and 45% ± 5% RH. Analysis of the water sorption of micronized salbutamol sulfate stored under these conditions is shown in Fig. 5. Initially, the relative humidity in the closed bag was very low. This can be explained by the adsorption of water to the amorphous areas on the particle surfaces. Within 5 days, ambient humidity was reached inside the bag. Because the relative humidity was less then 50%, the process of recrystallization took place only at a comparatively slow rate.

The recrystallization did not proceed as a cooperative process. Rather, the amorphous material assimilated water, recrystallized, and the desorbed water molecules were being assimilated by further amorphous regions. This mechanism can be deduced from the oscillating shape of the time course of relative humidity within the bag (Fig. 5).

An analogous storage experiment was conducted at the same temperature of 22°C ± 1°C but at a humidity level of 55%. Here, a clear difference in the sorption behavior was evident (Fig. 6). The relative humidity within the bag increased up to ~55%, followed by a rapid increase in humidity level up to 98%, and final adjustment to the equilibrium moisture content of ~55%. The rapid increase in humidity levels up to 98% was due to the recrystallization of the amorphous salbutamol sulfate in the presence of water, followed by the desorption of water after the recrystallization process. The decline of relative humidity after 2–3 days can be interpreted by the diffusion of water out of the PE-bag. Under such storage conditions, the sample was completely recrystallized within 1 week.

Thus, it has been shown that during storage of the micronized powder a "self-conditioning" process may occur. The rate of self-conditioning was dependent on the relative humidity in the storage chamber. Lower humidity led to an extended duration of the self-conditioning process. Furthermore, when particles were stored below a relative humidity of 50%, a significantly lower particle growth than particles that were stored above this humidity value was observed.

CONCLUSIONS

Sufficient conditioning of salbutamol sulfate ensured the complete and controlled conversion of amorphous parts into crystalline material and a stabilization of the powder. The physical stability of the micronized powder was influenced by the conditioning parameters. Dry conditioning has been shown to be useless in this regard. The relative humidity at room temperature should be at least 55% so that the powder will recrystallize within a period of 24 hr. This humidity level showed the smallest particle growth under the conditions tested. When shorter conditioning periods are desired, conditioning at 40°C and 75% RH have been shown to be alternative

Received Time Mar. 3. 2010 12:53AM No. 2379

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

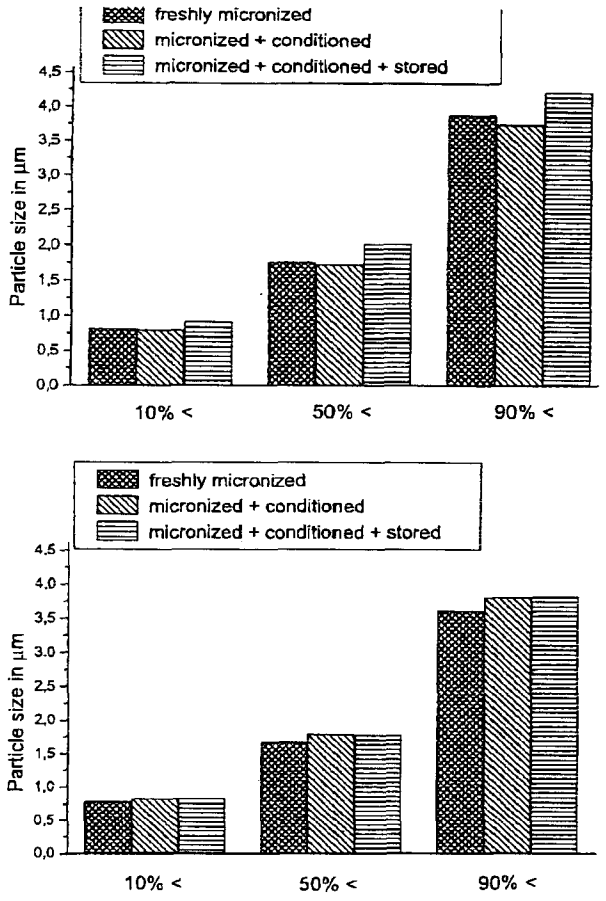


Figure 4. Particle size distributions of micronized, dry conditioned (upper figure) and humid conditioned (lower figure) salbutamol powder following storage for 4 weeks. The humid conditioning parameters were 21°C at 55% RH for 24 hr. The dry conditioning parameters were 70°C for 5 hr. The storage conditions were 22°C ± 2°C; 50% ± 8% RH. Approximately 50 g of salbutamol sulfate were stored in a PE-bag in each case.

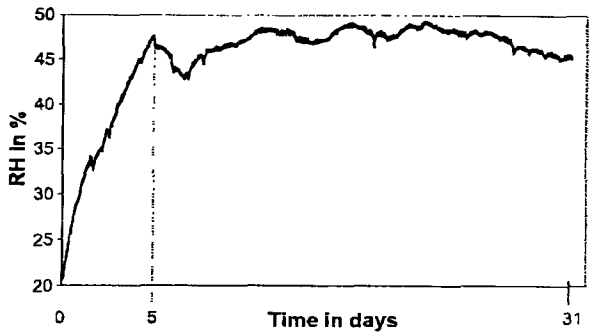


Figure 5. Relative humidity in a PE-bag filled with freshly micronized salbutamol sulfate powder and stored at relative humidity of 45%.

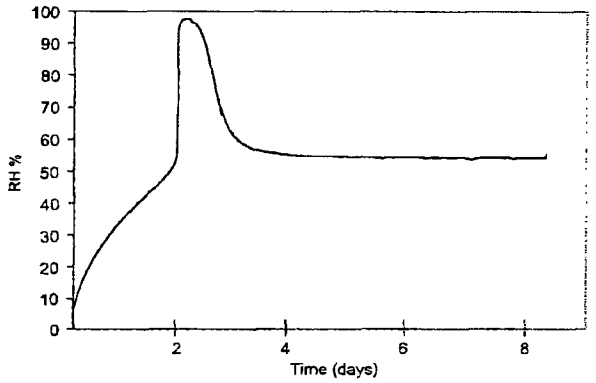


Figure 6. Relative humidity in a PE-bag filled with freshly micronized salbutamol sulfate powder and stored at relative humidity of 55%.

conditions to obtain a stable, entirely crystalline product.

The advantage of optimized conditioning process parameters is that every batch can be controlled to show a relatively small but acceptable particle growth. However, particle growth, cannot be completely prevented. The kinetics of the process is depending on the relative humidity, with higher humidities favoring faster rates. The extent of the agglomeration is dependent on the amorphous parts and, therefore, on the micronization energy, but also on the parameters of conditioning and storage. The use of nonconditioned material implies the inherent risk of its uncontrolled recristallization, which may occur at any time following milling (i.e., during storage of the milled material), formulation of the powder for dry powder inhalers, or following manufacture of the product even as late as in the hands of the patient.

REFERENCES

1. Threlfall, T.L. Analysis of organic polymorphs. Analyst **1995**, *120*, 2435–2460.
2. Briggner, L.-E.; Buckton, G.; Bystrom, K.; Darcy, P. The use of isothermal microcalorimetry in the study of changes in crystallinity induced during processing of powders. Int. J. Pharm. **1994**, *105*, 125-135.

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

3. Sebhatu, T.; Angberg. M.; Ahlneck, C. Assessment of the degree of disorder in crystalline solids by isothermal microcalorimetry. Int. J. Pharm. **1994**, *104*, 135–144.
4. Ticehurst, M.D.; Rowe, R.C.; York, P. Determination of the surface properties of two batches of salbutamol sulfate by inverse gas chromatography. Int. J. Pharm. **1994**, *111*, 241–249.
5. Yu, L. Amorphous pharmaceutical solids: preparation, characterization and stabilization. Advanced Drug Delivery Reviews **2001**. *48*, 27–42.
6. Ward, G.H.; Schultz, K. Process-induced crystallinity changes in albuterol sulfate and its effect on powder physical stability. Pharm. Research **1995**. *12*, 773–779.
7. Elamin, A.A.; Sebhatu,T.; Ahlneck, C. The use of amorphous substances to study mechanically activated materials in the solid state. Int. J. Pharm. **1995**. *119*, 25–36.
8. Hancock, B.; Zografi, G. Characteristics and significance of the amorphous state in pharmaceutical systems. J. Pharm. Sci. **1997**, *86*, 1–12.
9. Ahlneck, N.; Zografi, G. The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state. Int. J. Pharm. **1990**, *62*, 87–95.
10. Saleki-Gerhardt, A.; Ahlneck, C.; Zografi, G. Assessment of disorder in crystalline solids. Int. J. Pharm. **1994**, *101*, 237–247.

Pharmaceutical Solids—The Amorphous Phase

John F. Bauer

"Pharmaceutical Solids" discusses scientific principles associated with pharmaceutical solids useful to practitioners in validation and compliance. We intend this column to help the understanding of principles associated with pharmaceutical solids and to be a useful resource for daily work applications. Enhanced process understanding is an important objective of the quality-by-design initiative. The key objective for this column: Usefulness.

Reader comments, questions, and suggestions are needed to help us fulfill our objective for this column. Case studies illustrating principles associated with pharmaceutical solids submitted by readers are most welcome. Please send your comments and suggestions to column coordinator John Bauer at consultjb@comcast.net or to coordinating editor Susan Haigney at shaigney@advanstar.com.

KEY POINTS

The following key points are discussed:

- Definition of amorphous solid
- Meaning of long-range and short-range order in solids
- Disorder (amorphous nature) accelerates the rate at which the solid degrades, absorbs water, dissolves, etc.
- Small amounts of amorphous content can affect the properties of individual batches of drug
- The glass transition temperature (Tg) is a characteristic used to understand amorphous solids
- The Tg is the temperature at which an amorphous solid changes character from a glass-like solid to a more mobile rubbery state
- The higher the Tg, the more physically stable is the amorphous phase
- Using amorphous drug in a dosage form can often increase the rate of dissolution and consequently the bioavailability
- Amorphous content is very difficult to quantitate directly at levels that may be problematic
- The amorphous form of a drug should be characterized along with the crystalline forms during polymorphic screening.

INTRODUCTION

The concepts of solid forms and polymorphism have been discussed in a previous column (1). In review, pharmaceutical solids can exist in crystalline state in which the molecules are arranged systematically within the solid, forming a symmetric repeating pattern in which a single unit cell or building block is organized in three dimensions to construct the crystal. In "ideal" crystals, the atoms from the compound are arranged at regular intervals in each direction. This is assumed to extend indefinitely and homogeneously throughout the crystal. These solids are said to have long-range order. They are very stable systems with distinct physical properties.

In contrast, under certain conditions it may be possible to interfere with the compound's ability to organize with this long-range order. These compounds solidify in a disordered state as an amorphous solid. Amorphous solids are non-crystalline and have only some short-range molecular order similar in nature to the long-range order in the corresponding crystalline state.

Because the short-range order is similar to the order in one of the drug's crystal lattices and the drug may have several possible lattices (i.e., polymorphism), it is possible to have multiple amorphous forms depending

For more Author information, go to gxpandjvt.com/bios

ABOUT THE AUTHOR

John F. Bauer, Ph.D., is president of Consult JB LLC Pharmaceutical Consultants. Dr. Bauer has more than 30 years of pharmaceutical industry experience, including work in solid-state chemistry, analytical chemistry, stability, pharmaceutics, regulatory CMC, patents, and litigation. He may be reached at consultjb@comcast.net.

Received Time Mar. 3. 2010 12:53AM No. 2379

on how it is prepared. Any particular batch of drug can have varying degrees of disorder.

The amorphous state has been the subject of extensive research in the pharmaceutical field with the apparently opposing conclusions that it is a gift to the formulator and that it is the root of all evil.

The purpose of this column is to acquaint the reader with the amorphous state and its properties. The presence of the amorphous state should be considered when diagnosing manufacturing irregularities and when validating new processes and/or new sites.

AMORPHOUS SOLIDS

Amorphous material has not had the opportunity to arrange into a crystalline lattice. This means that the active sites that would be interacting with each other to build the crystal are now exposed more directly to the solids' environment. Therefore, any endothermic processes are not required to overcome lattice energy to proceed. In other words, the first step in most processes that involve crystals is to disrupt or destroy the stability of the crystal arrangement. This requires an input of energy that is not necessary when the amorphous form is involved.

Although the chemistry of amorphous and crystalline drug will be the same, the rate and ease with which reactions occur will be accelerated in the amorphous phase. This makes the amorphous phase of a drug less stable than the corresponding crystalline phase. For example, lactose is usually avoided in formulating amine-containing drugs because of the possibility of the well-known Maillard reaction between amines and sugars. This reaction is responsible for the non-enzymatic browning of some foods. Studies of this reaction using the amine containing drug metoclopramide and lactose as a model system indicate that higher reaction rates were found for amorphous samples of either the drug or lactose (2).

Obviously the difference in stability between amorphous and crystalline drug will depend on the innate chemistry of the drug molecule.

In addition to the reaction rate differences, the amorphous state differs from its crystalline counterpart in many physicochemical properties. Amorphous materials will by nature have higher surface area exposed to its environment. This is due to the fact that there is no three-dimensional structure limiting the available exposed surface. Surface area effects are, therefore, magnified in the amorphous state. Phenomena like hygroscopicity, air oxidation, adsorption on excipients, and/or instrumentation and blending effects are more problematic with amorphous drugs. Whereas the manufacturing and formulation processes using crystalline drug are reproducible, the same operations with an amorphous drug can require a great deal of external control.

Benefits of the Amorphous State to Formulations

One of the challenges facing drug discovery scientists is the discovery of pharmaceutical agents that have both acceptable pharmacologic activity and adequate aqueous solubility. In order for a drug to be effective it must be absorbed in the aqueous environment of the human body at concentrations high enough to be effective and at rates fast enough to avoid being eliminated prior to exerting its pharmacologic effects.

A large number of effective drug candidates being discovered in recent years have unacceptable solubility in the crystalline form. In order to address this problem, formulators have exploited the increased dissolution rates of amorphous phases. For example, the critically important AIDS medication ritonavir has very low solubility and is practically unavailable from the crystalline state (3). Formulators have been able to produce a formulation that maintains the drug in an amorphous phase and exploit the increased solubility and resulting increased bioavailability of the non-crystalline drug. This formulation approach has greatly benefited both formulator and patient by making available several important pharmaceuticals that would not have been available using crystalline drug. Amorphous phases can have varying levels of physical stability but are inherently unstable solid forms and will crystallize if conditions are right. What these conditions are needs to be well understood for any particular compound if it is going to be formulated as amorphous. These adverse conditions must be stringently avoided during manufacture and storage.

CHARACTERIZATION OF AMORPHOUS COMPOUNDS

From a pharmaceutical perspective, amorphous and crystalline drugs are opposites. "What is good for one is bad for the other." The Table contrasts the effect of the two solid phases on some physical and chemical properties of chemical compounds.

As a result of the lack of long-range order in the amorphous phase, there is an increase in molecular mobility. The molecules in the amorphous phase are not as mobile as when in the liquid state, but are significantly more mobile than in crystals. This

mobility allows molecules in the amorphous phase to slowly (or rapidly in some cases) rearrange themselves to attain long-range order and crystallize. This can make maintaining a compound in the amorphous phase very challenging—especially when maintaining the amorphous state is desired.

One parameter that can be used to characterize amorphous material is the temperature at which the molecular mobility changes significantly. This temperature is called the glass transition (Tg). At the Tg, the molecular mobility of the material is drastically affected. Below the Tg the molecular mobility is reduced to a glass-like solid. Above the Tg, however, the number and magnitude of molecular motions increase and, correspondingly, the ability to degrade and crystallize also increases. This makes determination of Tg critical for characterizing amorphous material. Thermal techniques such as differential scanning calorimetry (DSC) can be used to determine Tg. In the DSC, the glass transition appears as an endothermic heat capacity change reflected in a baseline step (Figure 1). The Tg of amorphous materials can vary in sharpness and, in some cases, can extend over a wide temperature range to hinder detection by DSC.

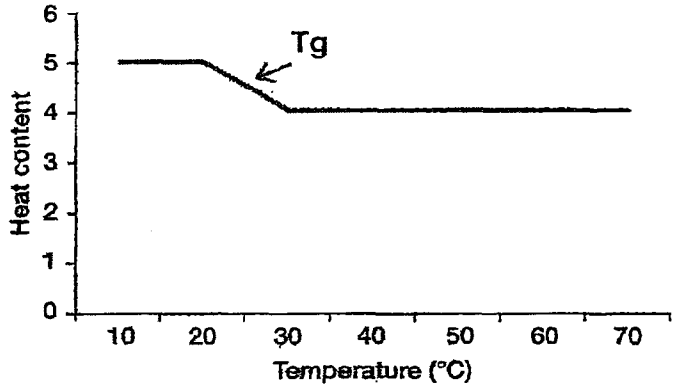
Unpredictability of Amorphous Content

A problem that is not often realized is that regardless of how stringent the crystallization process may be, it is practically impossible to manufacture a large-scale batch of drug substance without some amorphous content. This amorphous content may not be reproducible and will not be uniform within the batch. Although the chemistry and the physical properties of a particular active pharmaceutical ingredient (API) may be well characterized, its performance will vary somewhat from batch to batch due to this amorphous content. The amorphous component will dissolve quicker, wet differently, compress differently, and resist size reduction more than the crystalline drug. Depending on the amorphous content, batches of drug substance may vary somewhat in these properties. The rate of degradation may also vary with a trend as illustrated in Figure 2 (i.e., the degradation may appear biphasic due to the differing degradation rates of the amorphous and crystalline portions). Because of the variation in amount and distribution of amorphous material within a batch, it is important to examine batches of drug substance microscopically using a polarized light microscope. Although not quantitative, the presence of amorphous drug can be detected by polarized light microscopy. Amorphous drug does not exhibit birefringence (scattering of light) characteristic of crystalline material. This scattering results in characteristic colors as illustrated in Figure 3. Amorphous particles will not show these colors. The percentage of particles on a given microscope plate that do not exhibit birefringence can be an estimate of the amorphous content; although, the non-representative nature of the sample must be considered.

Table: Effect of amorphous and crystalline state on physico-chemical properties.

Property	Amorphous	Crystalline
Chemical stability	Decreases	Increases
Solubility rate	Increases	Decreases
Hygroscopicity	Increases	Decreases
Size reduction ability	Decreases	Increases
Wettability	Increases	Decreases
Hardness	Decreases	Increases
Molecular mobility	Increases	Decreases
Apparent solubility	Increases	Decreases
Physical stability	Decreases	Increases

Figure 1: Heat capacity vs. temperature at Tg in DSC.



AMORPHOUS FORMATION DURING PROCESSING

As mentioned previously, amorphous drug will be present in some amount in the active drug batch. If the manufacturing process is validated, the amorphous content should not vary dramatically from batch to batch unless changes are made in equipment and/or manufacturing site. There are, however, several

Figure 2: Typical degradation profile for mixture of crystalline and amorphous compound.

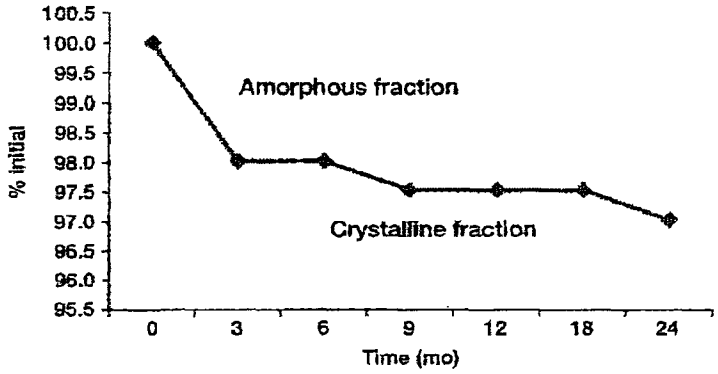
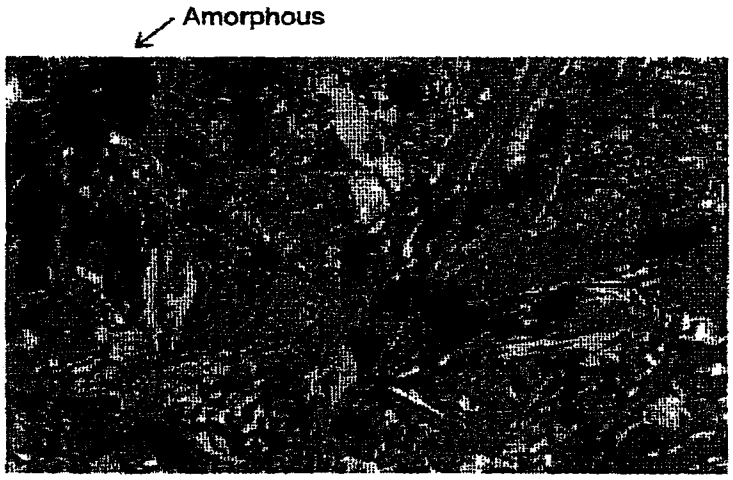


Figure 3: Example of birefringence under polarized light.



formulation processing unit operations that are able to convert crystalline drug to amorphous drug depending on the drug. Milling can reduce the crystallinity of a drug and create areas of disorder or amorphous regions; total change to the amorphous state is possible. Partial dissolution with rapid re-precipitation especially in non-aqueous or mixed solvents can produce amorphous compounds. Heating and cooling cycles especially near the melting point of the drug are also potential sources of amorphous transitions.

For example, Lefort et al. (4), using solid-state nuclear magnetic resonance (NMR) as a probe, demonstrated that the amorphous content of trehalose samples increased from 19.8 % after 5 minutes milling to 47.9% after 15 minutes of milling with the same intensity.

If the manufacturing process is not well controlled, changes in the amount of amorphous drug produced may occur, resulting in uncontrolled batch-to-batch variation. Effects of these changes may include the following:

- Differences in stability, both during and post manufacturing
- Differences in wettability, resulting in overmassing or undermassing
- Differences in compressibility leading to variability in tablet hardness.

QUANTITATIVE ANALYTICAL DETERMINATION OF AMORPHOUS CONTENT

Analytically amorphous is a negative phenomenon (i.e., it is the lack of the long range order that is present in crystals) and consequently is very difficult to detect or quantitate. Crystallinity is evaluated using a series of analytical techniques including x-ray diffraction, solid-state nuclear magnetic resonance, mid- and near-infrared spectroscopy, microscopy, and others. All of these techniques are in some manner responding to the short- and long-range order of the crystal structure; therefore, amorphous content shows little or no response. X-ray diffraction is the classic technique for determining crystal form and degree of crystallinity. The diffraction of x-rays by atoms that appear repeatedly in the same position within the unit cell as the symmetry extends indefinitely in three dimensions in a crystal is observed as a sharp peak at a characteristic two-theta position. In contrast, only the short-range order is detected in the amorphous phase. What is observed is a baseline hump or "halo" as illustrated in Figure 4.

The limit of quantitation (LOQ) for amorphous content in crystalline solids is approximately 10% by DSC and x-ray.

There are other physical techniques that can sometimes be used to estimate the amorphous content in a primarily crystalline sample. Spectroscopic techniques such as Raman, infrared, and near-infrared (NIR) spectroscopies will in some cases show peaks characteristic of the amorphous phase. The analyst can prepare a series of amorphous/crystalline mixtures and prepare a calibration curve of peak ratio versus amorphous content. In the case of cefazolin sodium, there is a characteristic amorphous peak at 1542/cm in the infrared. This peak can be used to estimate amorphous content using a ratio of 1542/cm to 1760/cm areas (5). The sensitivity of these techniques are better than x-ray but are in the range of 10%. Because the presence of amorphous in levels

lower than 1% can cause changes in the drug performance, these techniques are insufficient.

In some cases the difference in hygroscopicity between crystalline and amorphous compound can be exploited to quantitate the amorphous fraction. If the crystalline phase is non-hygroscopic or nearly non-hygroscopic, any water absorbed by a sample of the drug will be due to the amorphous content. Dynamic moisture sorption gravimetry (DMSG) determines weight gain at changing humidities. Figure 5 demonstrates the DMSG technique for determining amorphous content.

This technique can be very sensitive (<1%) when applicable.

Thermally stimulated current (TSC) monitors molecular matrices by subjecting the sample to an electric field at a fixed temperature. This results in an orientation of dipoles within the material. This orientation is then trapped by lowering the temperature. The temperature is then increased again resulting in a depolarization current that is plotted versus temperature. The limit of detection for amorphous content in mixtures has been reported as approximately 1% (6).

All of these techniques require the preparation of known mixtures of amorphous and crystalline drug to prepare a calibration curve and demonstrate the correlation between signal and amorphous content.

Because the direct detection of amorphous is so difficult, the approach that is often taken is to indirectly determine the amorphous content by determining differences and/or changes in drug crystallinity. In this approach, a lot of drug is established as a reference standard. Comparison of the area under the curve of the x-ray peaks, or the DSC melt endotherm, or the IR or NIR characteristic peaks of the unknown material are compared to the standard to determine percent crystallinity; the difference is inferred to be amorphous content. This technique suffers from the same lack of sensitivity and need for calibration curve that the direct methods do. However, the output signal that is being used is generally much more quantifiable.

Figure 4: Typical x-ray powder diffraction pattern of crystalline and amorphous drug.

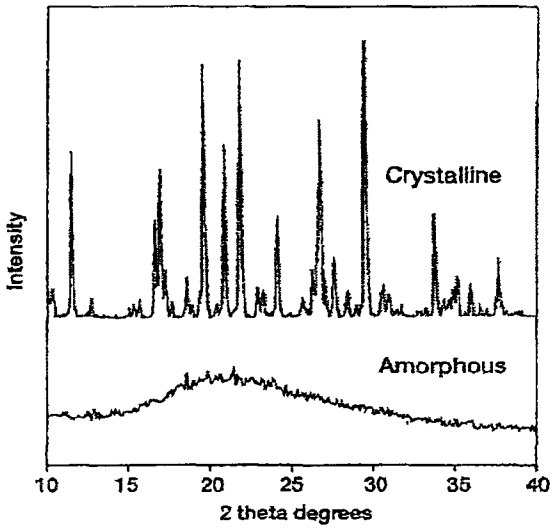
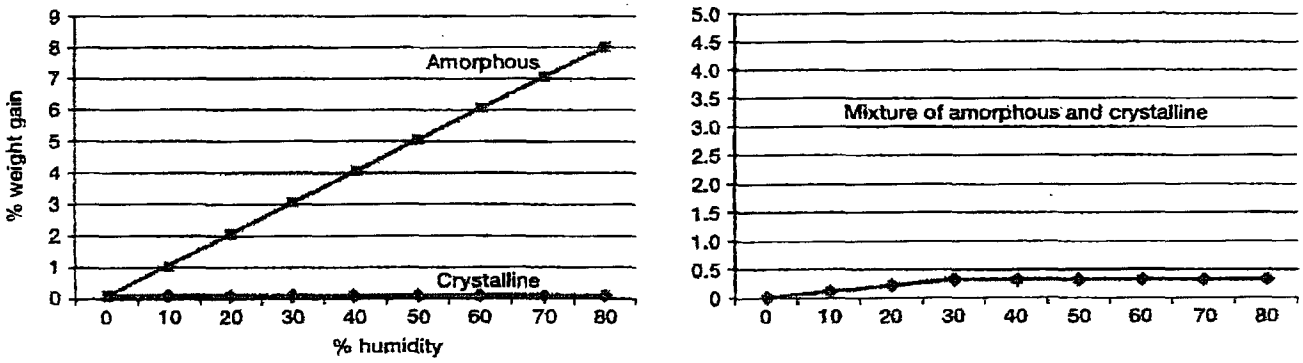


Figure 5: Typical DMSG plots of crystalline (non-hygroscopic) drug, amorphous (hygroscopic) drug, and a mixture of crystalline and amorphous drug.



Received Time Mar. 3. 2010 12:53AM No. 2379

CONCLUSIONS

Amorphous drug can be more or less invisible to the formulator and analyst until changes start occurring in the process or in product quality. Because the analytic techniques that can detect amorphous drug are insensitive and/or very time and labor intensive, it is not practical to establish specifications for amorphous drug. It is possible, however, to establish internal crystallinity requirements for the drug in order to avoid large amounts of amorphous content. It is imperative that efforts be made to determine Tg for the amorphous form of the drug. This will give the formulator a measure of the stability of the amorphous phase. Other studies should be performed to investigate the conditions that could convert the crystalline drug to amorphous. Some of this information can be obtained during polymorph screening. For example, solvent systems that produce amorphous drug can give an indication of the solvent types (ion strength, lipidity) that should be avoided in the processing. Dissolution and precipitation of drug from granulating fluid should be done to determine if amorphous drug would result when granulation is dried. Grinding and melt/cool studies should also be performed to determine the physical stage that results. Quantitation of the solubility and stability of the amorphous form of a drug candidate should be determined during preformulation studies to understand how the presence of amorphous could affect processing and performance. Once this information is available, the formulator and analyst should be open to considering the presence of amorphous drug when deviations are observed. If the drug product is an amorphous formulation, then similar studies should be performed to identify conditions that can cause crystallization.

Validation and compliance professionals must have a good understanding of the API and products for which they are responsible. This knowledge is critical in manufacturing process control, preventing manufacturing problems, and troubleshooting problem occurrences. Information from fundamental studies conducted during development of the API must be considered during routine commercial product manufacturing, especially when evaluating process changes as part of change control. Potentially a very simple change may cause unexpected effects on solid physical properties with very significant ramifications.

REFERENCES

1. Bauer, John F., "Polymorphism—A Critical Consideration in Pharmaceutical Development, Manufacturing, and Stability," *Journal of Validation Technology*, Vol. 14, #5, Autumn 2008.
2. Zhihui Qiu, "Effect of Pharmaceutical Processing on the Solid-State Maillard Reaction Between Metoclopramide Hydrochloride and Lactose Dissertation," Purdue e-Pubs.
3. H.L.Sham, C. Zhao, K.C. Marsh, D.A. Betebenner, S.Q. Lin, E. Mcdonald, S.Vasavanonda, N. Wideburg, A. Sadivar, T. Robbins, D.J. Kempf, J.J. Plattner, D.W. Norbeck, "Potent Inhibitors of HIV-1 Protease with Good Oral Bioavailability," *Biochem. Biophys. Res Commun.* 211: 159-165 (1995).
4. R. Lefort, A. De Gusseme, J.F. Willart, F. Danede, M. Descamps, "Solid State NMR and DSC methods for quantifying the amorphous content in solid dosage forms: An application to ball-milling of trehalose," *International Journal of Pharaceutics*, Vol. 280, pages 209-219, 2004.
5. B. Shah, V., Kakumanu, A. Bansal, "Analytical techniques for quantification of amorphous/crystalline phases in pharmaceutical solids," *Journal of Pharmaceutical Sciences*, Volume 95, #8, pages 1641-1665.
6. V.-P. Lehto and E. Lain, "Simultaneous Determination of the Heat and the Quantity of Vapor Sorption Using a Novel Microcalorimetric Method," *Pharmaceutical Research*, Volume 17, #6, pages 701-706(6), June 2000.

ARTICLE ACRONYM LISTING

API	Active Pharmaceutical Ingredient
DMSG	Dynamic Moisture Sorption Gravimetry
DSC	Differential Scanning Calorimetry
LOQ	Limit of Quantitation
NIR	Near-Infrared
NMR	Nuclear Magnetic Resonance
Tg	Transition Temperature
TSC	Thermally Stimulated Current